Remarks

Applicants respectfully request reconsideration in view of the following remarks.

Claims 1-34 were pending in this application. Claims 31-34 are withdrawn. Claim 1-30 are now pending and under examination.

In the Office Action, the Examiner stated that Applicants did not submit copies of all references listed in the Information Disclosure Statement filed August 13, 2003. The Examiner indicated that references E, P, R, S, W, Z and AA were not submitted. Applicants note that reference S is the Park reference (U.S. Pat. No. 5,762,903) and reference Z was the Lewis PCT reference (99 17812) both of which were previously submitted. Applicants direct the Examiner's attention to references E, R and W, which are listed on the accompanying form PTO-1449 (Exhibit A), and copies of which are attached hereto respectively. Copies of references P and AA are textbooks and are not being submitted.

In the Office Action, the Examiner stated that reference T appears to be particularly relevant, and that there was no date associated with this reference. Applicant states that this

reference reports on applicants' own work in connection with the subject matter disclosed and claimed. The publication date of reference T has been reported to be December 5, 2000, which is after the present filing date of September 8, 2000. Therefore, this document is not prior art under 35 U.S.C. §102.

The Examiner has rejected claims 1-30 as being allegedly obvious over Lewis et al (WO 99/17812) in view of Zamora et al. The Zamora reference has an apparent publication date of May 11, 2000. Applicants assert that the presently claimed invention of most of the claims was made by the applicants prior to May 11, 2000. Applicants submit the Joint Declaration of Judah Z. Weinberger, M.D., Ph.D. and Xin Qu, Ph. D. ("Dec.") which demonstrates that applicants had submitted a manuscript on March 23, 2000 to the J. Biomed. Res. which was accepted for publication on April 12, 2000. This manuscript has been previously submitted as reference T discussed above and was published on December 5, 2000. A copy of the published manuscript is attached as Exhibit 1 to the Weinberger Dec. The manuscript of Exhibit 1 describes experiments, all of which were performed prior to its acceptance date of April 12, 2000, and actually prior to the manuscript submission date of March 23, 2000, as attested to in the Dec.

The Exhibit 1 document describes an experiment wherein a poly (ethylene terephthalate) (PET) surface formed a substrate material, and a polymer layer of chitosan hydrogel was formed on the substrate material. The formation of the polymer layer on the substrate material was substantially free of inorganic polymers. The layer was then exposed to a radioactive isotope (^{32}P or o-phosphoric acid). The radioactive isotope was adsorbed in the layer. This procedure is discussed in the Materials and Methods section of the paper of Exhibit 1. This work was actually performed by co-inventor Xin Qu with the collaboration of Dr. Weinberger. The Weinberger Dec. states that an attempt to contact Dr. Qu in china has been unsuccessful.

The work described in Exhibit 1 demonstrates a reduction to practice of the subject matter of at least claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 22, 23, 26, 27, 28, 30 and 31.

While the submission of the Weinberger Dec. should be sufficient to overcome the Zamora reference for at least the claims listed above, applicant will address the rejection based on §103 on substantive grounds.

The Lewis reference, as the Examiner points out, does not disclose the use of a chelating or polymer layer on the substrate material. Accordingly, Lewis does not disclose a material formed of a polymer layer on a substrate material which is substantially free of inorganic polymers.

Applicants urge that it would not have been obvious to combine Lewis and Zamora because there would not have been any motivation to modify the Lewis reference. The Lewis reference states on page 11 that adsorption requires preconditioning with, for example, phosphoric acid, to convert the metallic surface of the wire through an oxidation process to a film or layer of oxide, phosphate or sulfate. There would be no motivation to do any further treatment to the wire if sufficient adsorption of Ce-144 or Ru-106 had been achieved, which was assumed to be the case.

The Zamora reference relates to putting a chelating microfilm on a metal layer before adsorption of a radioactive material of Re-188, which is different from Ce-144 or Ru-106 used in Lewis. Also, the chelating microfilm has not been shown to be a polymer.

Applicant urges that it would not have been obvious to combine Lewis and Zamora as proposed by the Examiner. Lewis relates to adsorption of Ce-144 or Ru-106 whereas Zamora relates to adsorption of Re-188. Further, as discussed above, Lewis nowhere indicates that he was unable to achieve adsorption of his radioactive material. Accordingly, there was no motivation to modify his steps to add another layer. In contrast, Zamora states in the Results section that he was unable to bind significant amounts of Re-188 unless he conjugated the chelating microfilm to the wafer, so he was motivated to apply the chelating microfilm, but there is no indication that Lewis needed any chelating microfilm in his process.

Moreover, even if one was hypothetically motivated to combine Lewis with Zamora and decided to selectively use the chelating microfilm, this microfilm has not been shown to be a polymer as recited in claim 1.

Independent claim 22 also recites a polymer layer on a substrate material, as independent claims 25, 26, 27, 28, 29 and 30. The other claims under consideration are dependent. These dependent claims should be patentable for at least the same reasons.

For at least this reason, applicant respectfully requests withdrawal of the §103 rejection and allowance of all of the claims.

No fee other than the $180 fee for the Supplemental Information Disclosure Statement, a check of which is enclosed is believed to be due in connection with this Communication. If any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account Number 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Peter J. Phillips
Registration No. 29,691
Attorneys for Applicant
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

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Peter J. Phillips Date
Reg. No. 29,691

Novel β-emitting poly(ethylene terephthalate) surface modification

Xin Qu, Judah Weinberger
Interventional Cardiology Center, Departments of Medicine and Pharmacology, Columbia University, 161 Fort Washington Avenue, AP-551, New York, New York 10032

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Abstract: Restenosis after percutaneous interventions in coronary and peripheral arteries leads to repeat procedures and surgery in a significant number of patients. We have previously demonstrated that irradiation of an arterial site using an endovascular source (brachytherapy) is highly effective in preventing the restenotic process. To this end, a novel beta radiation delivery system was developed, based on the adsorption of ^{32}P (o-phosphoric acid) by pH-sensitive chitosan hydrogel on a poly(ethylene terephthalate) (PET) balloon surface. The PET balloon surface was treated with oxygen plasma and coated with chitosan hydrogel. Covalent bonds, ionic bonds, and hydrogen bonds all contribute to the adhesion between chitosan hydrogel and PET. In the aqueous phosphoric acid (PA) solution, the $-NH_2$ groups of chitosan were protonated by PA and the adsorption of PA occurred at the same time. The effect of PA concentration and temperature on adsorption efficiency and kinetics were studied. More than 70% PA was adsorbed on the sample surface in 0.2 m*M* PA solution. The surface of samples was also investigated by attenuated total reflection–Fourier transform infrared spectroscopy and scanning electron microscopy. PET surface may be modified to carry high activity beta emitters; such materials may be useful in a therapeutic setting. © 2000 John Wiley & Sons, Inc. J Biomed Mater Res, 52, 492–497, 2000.

Key words: brachytherapy; intracoronary radiation; PET; balloon; chitosan; o-phosphoric acid; D,L-lactic acid; surface modification

INTRODUCTION

Balloon angioplasty and stent implantation are widely applied therapies for symptomatic, obstructive atherosclerotic coronary artery, and peripheral arterial disease. A major source of morbidity, and a major remaining limitation, restenosis rates are as high as 30 to 50% with these procedures.[1,2] Pharmacological and mechanical approaches to restenosis prevention thus far have been disappointing.[3,4] The impact on restenosis achieved with intracoronary stents is blunted because of a persistent neointimal proliferative response. We have demonstrated previously the ability of intravascular sources of ionizing radiation to prevent neointimal proliferation in models of restenosis. Intravascular radiation therapy, or brachytherapy, seems to prevent restenosis by reduction of smooth muscle cell proliferation, matrix formation, and by minimizing the late constriction of the vessel wall. The effects of ionizing radiation on cell proliferation and vascular remodeling were demonstrated previously in several animal studies[5–9] and in early clinical trials.[10–12]

A number of platforms have been devised to deliver brachytherapy from catheter-based systems (high-dose rate) or radioactive stents (low-dose rate). Beta-emitters delivered by catheter-based approaches include ^{90}Y wire sources (Schneider), encapsulated $^{90}Sr/Y$ (Novoste), and ^{32}P seeds (Guidant), and ^{188}Re as a solution source for balloon inflation.[13] ^{192}Iridium, a gamma emitter, is being developed in wire-affixed seed geometry (Cordis J & J). For reasons of shielding and patient and operator safety, a clear preference exists for beta sources, although the relative efficacy of various isotopic sources is still under investigation.

Chitosan, (1,4)-2-amino-2-deoxy-β-D-glucan, is a natural polymer generally obtained by extensive deacetylation of chitin isolated from crustacean shells. Because of its special biological, chemical, and physical properties, chitosan and its derivatives have applications in many industrial, agricultural, and biomedical activities.[14,15] Chitosan hydrogels synthesized from chitosan and D,L-lactic acid have been reported in the literature.[16,17] The free amino groups and porous structure of chitosan hydrogels provide them the

Correspondence to: J. Weinberger; e-mail: jzwl@columbia.edu

ability to adsorb o-phosphoric acid (PA) in aqueous solution.

In this article, we report a novel beta radiation delivery material that may be useful in a particularly simple brachytherapy delivery system, based on the adsorption of ^{32}P (o-phosphoric acid) by a chitosan hydrogel on poly(ethylene terephthalate) (PET) surface. PET surface is found in existing angioplasty balloons, and could also be used in wire geometry. We investigate the variables affecting both efficiency of isotope uptake and surface capacity, as well as the morphology of the surface.

MATERIALS AND METHODS

Chitosan (M_w = 150 kD) from Fluka (Buchs, Switzerland) and D,L-lactic acid (85%) from Fisher Scientific (Pittsburgh, PA, USA) were used for preparation of chitosan hydrogel. O-phosphoric acid (85%) (Fisher Scientific, Pittsburgh, PA) was used for adsorption experiment. ^{32}P-o-phosphoric acid (8500–9120 Ci/mmol, 10 mCi/mL) (NEN, Boston, MA) was used for measuring adsorption efficiency and kinetics by liquid scintigraphy. Ecoscint A was obtained from National Diagnostics, Inc. (Atlanta, GA, USA). PET balloons (15 × 55 mm) were obtained from Advanced Polymers, Inc. (Salem, NH, USA).

Surface modification of PET balloons by chitosan hydrogel

PET balloons were treated by oxygen plasma to obtain hydrophilic surfaces. The PET balloons were then cut into small pieces (5 × 10 mm, thickness 30 ± 2 μm). These PET films were coated on one side surface by 1% chitosan/D,L-lactic acid solution, which was prepared by dissolving chitosan powder in D,L-lactic acid aqueous solution with the weight ratio of chitosan/lactic acid = ½. The coated films were dried in an oven at 80°C for 1 h. The thickness of the coated films was 31 ± 2 μm. The synthesis and characterization of these chitosan hydrogels have been described previously.[16,17]

Adsorption of PA by hydrogel layer

Coated films were immersed in varying concentration of the trace ^{32}P radiolabeled o-phosphoric acid aqueous solutions (0.5 mL) at room temperature or at 50°C. The adsorption efficiency and kinetics were computed by measuring the residual ^{32}P in the adsorbing solutions. Adsorption efficiency of samples at time t was calculated by the following equation:

$$\text{Adsorption efficiency (\%)} = (M_0 - M_t)/M_0 \ (\times 100)$$

where M_0 and M_t are the amount of PA in solutions before the adsorption (M_0) and after the adsorption at time t (M_t).

Characterization

Fourier transform infrared (FTIR) transmission spectra were obtained using the attenuated total reflection (ATR) technique. The surfaces were analyzed on a Perkin-Elmer 2000 infrared Fourier transform spectrometer. Scanning electron microscopy (SEM) analyses were performed using a Jeol JSM-5600LV scanning electron microscope (Japan). Samples were mounted on metal stubs and sputter-coated with gold-palladium. A liquid scintillation counter from LKB Wallace, 1209 Rackbeta, was used to measure the concentration of the ^{32}P isotope in the solution before and after the adsorption. A 10-μL solution was taken and mixed with a 5-mL scintillation solution. The thickness of the films was measured with a micrometer caliper.

RESULTS

Chitosan hydrogel layer on PET balloon

Untreated PET balloon surface is hydrophobic. After oxygen plasma treatment, the surface becomes hydrophilic. Figure 1(A) shows the morphology of the plasma-treated PET film. The parallel lines on the surface reflect the manufacturing process. After coating with chitosan hydrogel, the PET film became much smoother and a thin layer, about 1μm, appeared on the surface [Fig. 1(B)]. Figure 2 shows the ATR–FTIR spectra of the untreated and oxygen plasma-treated PET film. Compared with the spectrum of the untreated sample in Figure 2(A), the oxygen plasma-treated sample [Fig. 2(B)] has two new small peaks appearing at 3610 cm^{-1} and 3530 cm^{-1} which are attributed to the –COOH and –OH groups formed on the surface by oxygen plasma treatment. As shown in Figure 3(A), these two peaks were overlapped by a broad peak at 3250 cm^{-1} assigned to the chitosan hydroxyl groups, after the chitosan hydrogel was coated on the surface. In addition, a new peak corresponding to free amino groups of chitosan appeared at 1563 cm^{-1} and the peak at 1067 cm^{-1} was assigned to the chitosan saccharide structure.

Adsorption of PA

After the chitosan hydrogel coated film was immersed in 2 mM of PA solution for 2 h and dried; the ATR–FTIR spectrum of the sample surface was measured. Two new and strong peaks (1609 cm^{-1} and 1530 cm^{-1}), that are related to the deformation of NH_3^+ groups in chitosan, appeared in the spectrum [Fig. 3(B)]. The $-PO_4$ vibration peaks are predominant compared with the existing chitosan peaks. The absorption

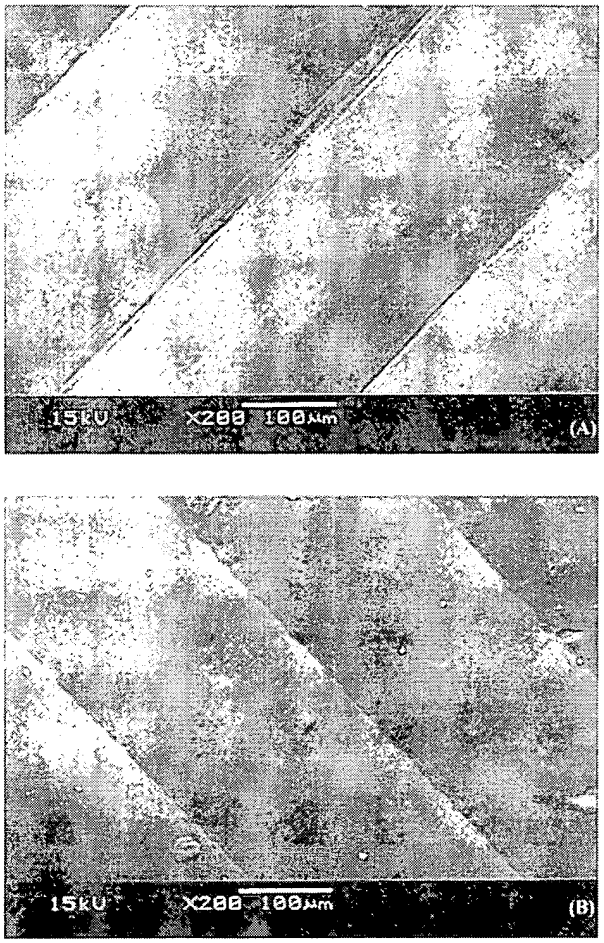

Figure 1. SEM photographs of (A) oxygen plasma-treated PET surface and (B) chitosan hydrogel-coated PET surface.

peaks at 1130 cm^{-1} and 1020 cm^{-1} are due to the P–O stretch. Meanwhile, the peak of hydroxyl group at 3250 cm^{-1} increased after forming the chitosan phosphate. Figure 4 shows the SEM photograph of the film after the adsorption. The film is a little rough as compared with the CS-coated film and with some small white particles on the surface. The upper left corner displays disruption of the chitosan coating caused by handling. This allows an estimate of the film thickness to be approximately 1 μm.

Adsorption efficiency of chitosan hydrogel layer

The PA adsorption efficiency of the treated PET surface was examined at room temperature and at 50°C as a function of PA concentrations. All data were measured after the samples were immersed in the solutions for 2 h. As shown in Figure 5, the adsorption efficiency of PA increases with the decrease of solution concentration and reaches maximum at 0.2 m*M*. In

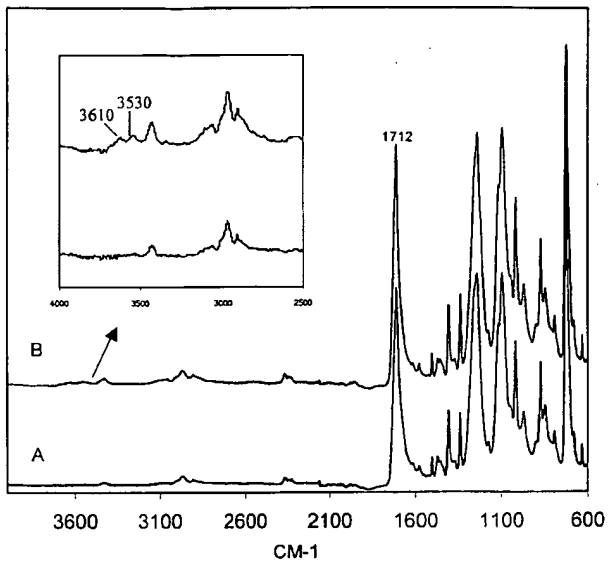

Figure 2. ATR–FTIR spectra of (A) untreated PET surface and (B) oxygen plasma-treated PET surface.

general, the efficiency values at 50°C are higher than those values at room temperature, whereas two curves have the same trend. As shown in Figure 6, the amount of H_3PO_4 adsorbed on the sample surfaces increases with the increase of the solution concentration. Both curves level off at 5 m*M* because of the saturation of H_3PO_4 adsorbed on sample surface. The film adsorbed more H_3PO_4 at higher temperature.

Figure 7 presents the adsorption kinetics of samples in different PA concentrations at room temperature. It is clear that the adsorption efficiency notably depends on the solution concentration and the adsorption time.

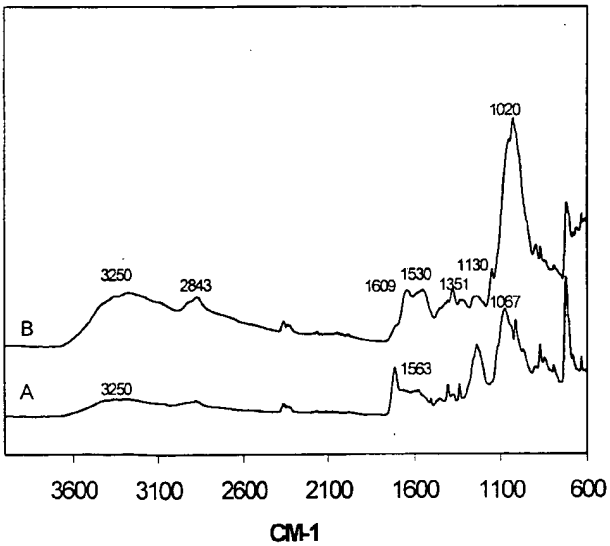

Figure 3. ATR–FTIR spectra of (A) chitosan hydrogel-coated PET surface, (B) the coated PET surface after adsorption in 2-m*M* PA solution for 2 h.

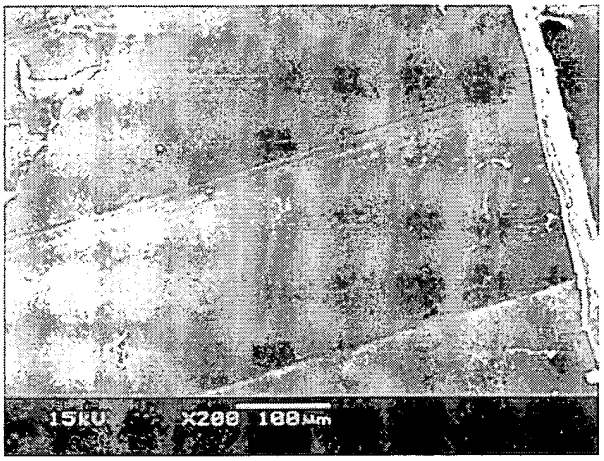

Figure 4. SEM photographs of chitosan hydrogel-coated PET balloon surface after adsorption in PA solution for 2 h.

The higher the concentration of PA solutions, the lower the adsorption efficiency, but the time to equilibrium is much shorter. In all cases, the equilibrium adsorption was almost reached within 2 h.

DISCUSSION

Chitosan hydrogel could not be attached to the untreated PET balloon surface because untreated PET is hydrophobic. After the oxygen plasma treatment, functional groups such as –OH and –COOH were created on the sample surface. As illustrated in Figure 8, a chitosan hydrogel coating could be expected because of the formation of covalent bonds, ionic bonds, and

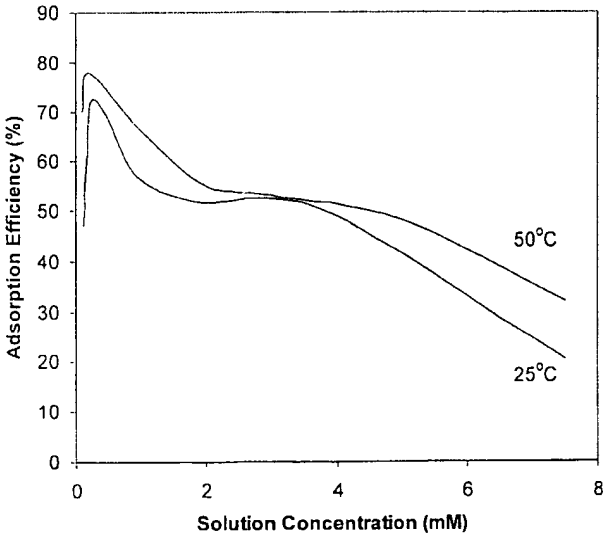

Figure 5. The effect of temperature and solution concentration on sample adsorption efficiency.

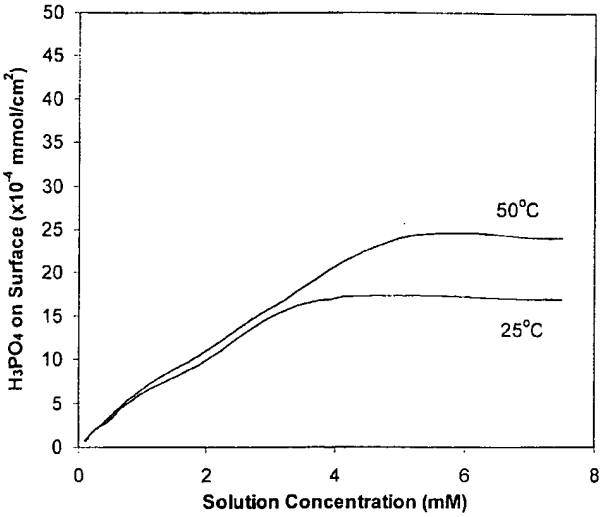

Figure 6. The effect of temperature and solution concentration on the amount of PA adsorbed on the sample surface.

hydrogen bonds between the functional groups on the surface and $-NH_2$ groups of chitosan during the heating process. A similar method has been used to coat polypropylene films with chitosan for improving dyeing behavior.[18]

As shown previously,[16,17] aqueous solutions of chitosan and lactic acid can form hydrogels after heating. Chitosan is first dissolved in lactic acid solution to form chitosan lactate salt. The dehydration of chitosan lactate salt will occur to form amide groups during heating. Simultaneously, the polycondensation of lactic acid occurs to form lactic acid side chains. The formation of chitosan hydrogel is due to the physical crosslinking through hydrophobic side chains aggregation and intermolecular interactions by hydrogen bonds between side and main chains, which eventu-

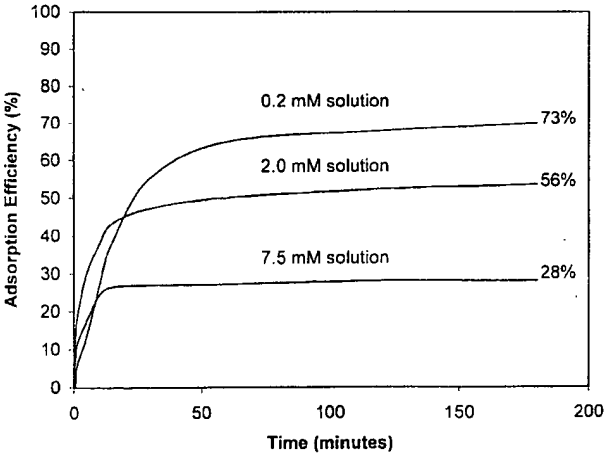

Figure 7. The adsorption kinetics of samples in the PA solutions with different concentrations at room temperature.

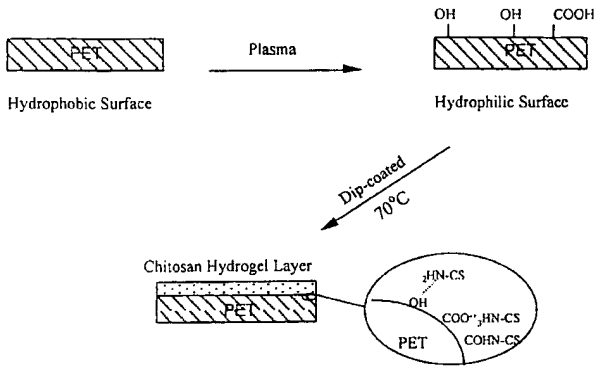

Figure 8. Surface modification of PET balloon by chitosan hydrogel.

ally lead to a corresponding decrease of chitosan chain mobility in the aqueous solutions.

The chitosan hydrogel layer on the PET surface is smooth and transparent. It is pH sensitive and swells extensively in aqueous PA solution. The unreacted amino groups of chitosan are ionized by the PA, and the acid attached to the gels by the ionic bonds. The influence of H_3PO_4 concentration on the adsorption efficiency could be divided into three periods. At concentrations higher than 5-m*M* solutions, the hydrogel layer adsorption was maximal at 1.8×10^{-3} mmol H_3PO_4/cm^2 at 25°C and 2.5×10^{-3} mmol H_3PO_4/cm^2 at 50°C, which is independent of the concentration. The adsorption efficiency decreases with the increase of the concentration. In the solution concentration between 0.2 m*M* and 5 m*M*, the hydrogel layer adsorbed more at higher H_3PO_4 concentration, whereas the adsorption efficiency decreased with the increase of concentration. The efficiency reaches the highest values (70–80%) at 0.2-m*M* solution. Below this concentration, the adsorption efficiency decreases with the concentration. As indicated in Figure 7, the adsorption process is always faster in higher H_3PO_4 concentration solutions.

Radiation dosimetry is critical in vascular brachytherapy. Overdose and underdose could result in reduction of the treatment effectiveness and may increase the radiation toxicity. The radioisotope capacity of this system has been computed as follows. The carrier-free activity of ^{32}P isotope we used is 8500–9120 Ci/mmol, so the maximum achievable activity density is 20 Ci/cm^2 on the PET surface. Typical activities needed for the intracoronary radiation is about 20 mCi/cm^2 for a 2-cm treatment length. This calculation indicates that surface capacity is approximately 1000-fold greater than required.

The feasibility of providing uniform dosimetry is also critical in vascular brachytherapy. In usual wire-based delivery procedures, the source is not centered in available lumen. The lack of centering may be associated with overdosing on one side of the vessel wall and underdosing on the other side. In this case, the use of a radioactive balloon surface would provide the best attainable uniformity of dose at the arterial wall even if the balloon or vessel takes a turn. Another configuration of the radioactive surface allowed by the high capacity for radioisotope would be as a flexible polymer wire coated with the radioisotope.

When the radioactive balloon is inserted into the body, it is absolutely necessary to make sure the isotope will not elute from the balloon into aqueous environment by the blood. The control of ^{32}P-PA off-rate in aqueous solutions by additional coatings is now under investigation and will be reported separately.

We have examined the capacity of approach described herein to other radioisotopes and other polymer surfaces. The surface modification of nylon balloon after plasma treatment was also achieved by this method and similar results have been obtained in our laboratory (data not shown). Meanwhile, the chitosan hydrogel on the surface has the ability to chalet radioisotope ions such as ^{188}Re, which provides another alternative to radioactive balloon surface (data not shown).

CONCLUSION

A novel beta radiation delivery system was developed for intracoronary radiation, which is based on the adsorption of ^{32}P (o-phosphoric acid) by pH-sensitive chitosan hydrogel on PET balloon surface. The radiation dose of the balloons could be manipulated by changing the ^{32}P concentration in the solution and also the proportion of cold and hot PA. The control of ^{32}P-PA off-rate in aqueous solutions from this system requires further study.

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